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SOME NEWER CONCEPTS IN DIGITALIS THERAPY.*

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Not quite twelve years ago Mackenzie published his epoch-making work on *Diseases of the Heart,* which marked the beginning of a revolution in our knowledge of the physiology and pathology of that important organ. At about the same time Einthoven brought forth his string galvanometer as a clinical instrument for the scientific study of the mechanism of the heart-beat; and through the work of Mackenzie the polygraph had become an instrument of great clinical value. We were thus, all at once, provided with a new outlook upon the functions of the heart in health and disease and with instruments of precision for the study of these functions. During this brief span of years our knowledge of the heart's normal and pathologic physiology has been advanced far more than it had in the preceding century, and with this advance there came the opportunity for the more accurate investigation of the action of drugs upon the heart in man. Many such investigations have been made with reference to the actions of digitalis and the digitalis bodies, and it is with the results of some of these that the present paper is concerned.

Slowing of the heart has been regarded as one of the characteristic actions of digitalis in man ever since it was first observed by Withering. The most superficial observation should have revealed

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that this action often fails to appear even when the administration of digitalis is followed by beneficial effects. We now know that the only large group of cases in which digitalis produces marked reduction in the heart-rate is that of auricular fibrillation. With but two exceptions the therapeutic administration of digitalis is seldom followed by a significant degree of slowing of the heart-rate in the presence of the normal sinus rhythm. The two exceptions are those cases of heart-failure in which marked edema is present and those with hypodynamic, unstable hearts in which the rate is generally rapid but is subject to spontaneous fluctuations. In both of these digitalis generally produces considerable slowing. Finally, slowing of the heart is seen in man not infrequently as one of the common manifestations of digitalis intoxication, when it is due to the production of some degree of heart-block. When the normal sinus rhythm is present, therefore, slowing cannot be regarded as one of the primary characteristic therapeutic actions of digitalis. The recognition of this fact is of considerable therapeutic importance, for it reveals the fallacy of one of the chief objections advanced against the administration of digitalis in cases of heart failure due to aortic insufficiency, and recent clinical experience has shown that digitalis is not only not contra-indicated in such cases but is often of great value for the relief of the failure. It should be said, however, in this connection that heart-failure does not usually result from aortic insufficiency until a late stage, when the contractile power of the ventricular musculature has been greatly exhausted. Therefore, while digitalis is not contra-indicated its administration not infrequently fails to relieve the heart-failure. There is no satisfactory evidence, however, that its judicious employment is ever harmful in such cases, and it should always be given a trial.

The mechanism by which digitalis produces slowing of the heart has been the subject of recent investigation, especially by Cushny, Marris and Silberberg,[1] Cushny[2] and others. It has long been known, as demonstrated in animal experiments, that digitalis stimulates the vagus center in the medulla and thereby reduces the rate of the heart in one of two ways: Either the rate of the whole heart is diminished by depression of the rate of impulse formation in the sinus or the rate of the ventricles alone is reduced through depression of auriculoventricular conduction to a degree sufficient to cause partial or complete heart-block. The former, slowing of the whole heart, is the type commonly found in patients presenting the normal sinus rhythm—that is, in patients with the hypodynamic heart and in those with edema. The latter, as has been mentioned, is commonly a manifestation of minor intoxication by digitalis, and also occurs chiefly in hearts with the normal rhythm.

[1] Action of Digitalis in Therapeutics, Heart, 1912–13, iv, 33.
[2] Digitalis in Auricular Fibrillation, Jour. Pharm. and Exp. Therap., 1918, ii, 103.

It has been said that digitalis is contra-indicated in cases of partial heart-block, and in those in which there is evidence of impaired conduction, as shown by prolongation of the *A–V* or *P–R* intervals. It has also been stated that marked prolongation of conduction time and partial heart-block occur in man from the use of digitalis only in cases previously showing some impairment of conduction. Neither of these contentions is wholly correct. Extensive clinical observations have shown conclusively that while there is an increased tendency for digitalis to enhance a preëxisting depression of conduction or partial block it is by no means contra-indicated in cases of this type. In many such cases it may be administered with satisfactory results without further prolongation of conduction time or increase in heart-block. In others the block, or impaired conduction, seems to be largely secondary to the existence of the heart-failure, and when digitalis relieves the failure the block may disappear or the conduction time may be shortened. Finally, if the administration of digitalis does show a tendency to increase an existing impairment of conduction this can generally be overcome by the administration of suitable doses of atropin to depress the cardiac endings of the vagus and thereby remove the effects of the central stimulation. While digitalis is not contra-indicated in cases with impaired conduction it should always be administered with caution and the patient should be observed at frequent intervals, always with the aid of instrumental methods if possible, to detect at once any increased depression of conduction should it develop.

The belief that therapeutic doses of digitalis do not frequently depress conduction in man unless there is an existent impairment of this function has been overthrown by Cohn[3] and by White and Sattler,[4] who have shown that some delay in conduction time is an almost invariable phenomenon of digitalis action even in normal persons. It is true, however, that the depression is not usually very marked until the stage of minor digitalis intoxication is reached. The prolongation of conduction time may progress gradually during the administration of digitalis or it may develop suddenly. It seems quite probable that the delayed conduction may constitute an action of digitalis which is of some therapeutic value in cases in which the rate of the heart is not altered even though the delay be small. The interval between the auricular and the ventricular contractions is increased by the time by which conduction is prolonged, and even when this does not exceed 0.02 of a second it means a considerable increase in the time allowed for the auricles to empty into the ventricles. This should be quite sufficient to increase

[3] Clinical and Electrocardiographic Studies on the Action of Digitalis, Jour. Am. Med. Assn., 1915, lxv, 1527.

[4] Effect of Digitalis on the Normal Human Electrocardiogram, with Especial Reference to A–V Conduction, Jour. Exp. Med., 1916, xxiii, 613.

materially the amount of blood flowing into the ventricle, especially in cases of mitral stenosis, and thereby improve the circulation.

Recognition of the capacity of digitalis to depress auriculoventricular conduction through stimulation of the vagus center and the discovery of the fact that its striking capacity to slow the ventricular rate in auricular fibrillation is due to the blocking off from the ventricles of many of the feebler auricular impulses, led to the tacit assumption that this block was also dependent upon central vagus stimulation. Cushny and his associates, however, observed that the block produced in auricular fibrillation, unlike that in the regular heart, could not in many cases be abolished by depression of the vagus endings in the heart by atropin. That is, they found that before digitalis was given the administration of atropin produced a greater acceleration in ventricular rate than followed the same dose when given after the ventricles had been slowed by digitalis. They thereupon investigated the mechanism of the slowing produced by digitalis in man, in intact animals and in perfused, isolated animals' hearts, and concluded there are two types of mechanism by which this is accomplished. Type A is purely inhibitory through central vagal stimulation; it can be antagonized by paralysis of the vagus endings with atropin; and it is the mechanism commonly found in the presence of the normal sinus rhythm. Type B is the result of a direct action of digitalis on the conducting tissues to depress their functions; it is unaffected by atropin; and it is the mechanism involved in most cases of auricular fibrillation and in rare instances when the rhythm is normal. It occurs typically in animal hearts which have become malnourished by long perfusion, and Cushny suggests that it rests largely upon the existence of malnutrition. He believes that it is common in auricular fibrillation because that condition especially favors the development of malnutrition of the human heart.

The accuracy of Cushny's observations is not to be doubted, but we believe that his conclusions are too sweeping. In the first place Cushny's own observations do not seem to exclude all participation of the vagus inhibitory action, for while he shows that the administration of atropin produces a greater acceleration in ventricular rate, both actual and proportional, when the heart is not slowed by digitalis than when it is, his records also show that atropin does accelerate the rate even when it has been greatly slowed by digitalis. This seems to indicate the existence of some vagal inhibition, and his arguments to the contrary are not altogether convincing. Further, his contention that the slowing is produced by a direct action of digitalis upon the junctional conducting tissues does not seem to have been proved by his experiments, although the action is evidently upon some structure distal to the vagal endings. Cohn

and Fraser[5] have shown that even when the administration of atropin fails to restore the heart-rate to its previous level after it has been slowed by digitalis the atropin, nevertheless, always removes completely whatever delay in conduction the digitalis may have produced. The whole matter is in need of further investigation.

So much for the mechanism by which digitalis slows the human heart, let us now briefly consider the therapeutic value of reducing the rate of the ventricles or of the whole heart. We have already indicated how simple prolongation of conduction time may be of value in mitral stenosis. Reduction in the rate of the heart, or that of its ventricles, is accompanied by a lengthening of the diastolic or resting-phase of the ventricles, while the duration of the systolic-phase is but little altered. This lengthening of diastole allows a larger volume of blood to flow into the ventricles and gives time for a more complete recovery of their contractile power. The force and volume output of ventricular systole are thus increased, and since more blood is thrown into the aorta and diastole is prolonged, coronary circulation is increased, the nutrition of the ventricular musculature is improved and internal respiration is more perfect in the ventricles. These secondary results are especially pronounced in cases of auricular fibrillation because of the added fact of the elimination of the frequent abortive ventricular contractions which exhaust the contractile power and do not contribute materially to the nutrition of the ventricular musculature. It should be mentioned in this connection that while digitalis so effectively slows the ventricles in auricular fibrillation the rate and the fibrillation of the auricles are not altered.

While slowing alone can account for all of those beneficial effects of digitalis in man which lead to the restoration of the failing heart and secondarily to the disappearance of the patient's symptoms, it is far from being a constant effect. The contention that the beneficial effects of the administration of digitalis are wholly attributable to its capacity to slow the heart is not supported by the facts, for there are many cases in which digitalis is quite effective in restoring the failing heart, although it does not alter its rate. The experiments of Gottlieb and Magnus[6] and others, on the isolated perfused heart, demonstrate that digitalis is capable of producing a marked increase in the volume output of the ventricles per beat, both by increasing the extent of diastolic filling and the completeness of systolic emptying. They also show that the force of ventricular systole is markedly increased by digitalis. These actions are necessarily exerted directly upon the ventricular musculature, since they occur in the heart after its removal from the body. Francois-

[5] Certain Effects of Digitalis on the Heart, XVIIth Int. Cong. Med., 1913, Medicine.

[6] Digitalis und Herzarbeit, Arch. f. exp. Path. and Pharm., 1904, li, 30.

Frank observed similar results from the administration of digitalis to living animals. These experiments suggest the existence of a similar direct action of digitalis on the human heart to increase the force and volume of ventricular systole. Although there are no methods available for proving the existence of such an action in man, it seems highly probable that it does occur for the following reasons: In the first place the alterations in the T wave of the electrocardiogram, which Cohn, Fraser and Jamieson[7] have shown to occur commonly early in the course of the administration of digitalis to man, are apparently due to a direct action of the drug upon the myocardium. Cushny's observations previously discussed also seem to prove that digitalis exerts a considerable direct myocardial action in man, and there is every reason to believe that the production of ventricular premature contractions by digitalis is the result of a direct muscular action. There is evidence, therefore, that digitalis does act directly upon the human myocardium. In the second place we know that digitalis is capable of relieving heart-failure and restoring cardiac efficiency in cases in which it produces no slowing, and even in cases of complete heart-block. It is impossible to account satisfactorily for its effects in such cases except by assuming that it increases the force or magnitude, or both, of ventricular systole.

We have seen that digitalis may exert one or more of the following actions in man when administered in therapeutic doses:

1. It may slow the rate of the whole heart through stimulation of the vagus center.
2. It may prolong the time of auriculoventricular conduction through a similar action.
3. It may slow the rate of the ventricles, either by the production of some degree of heart-block through central vagal stimulation or by virtue of some direct action on the heart.
4. It seems probable that it may exert a direct action on the myocardium which results in an increase in the force or magnitude, or both, of ventricular systole.

These, and these alone, seem in the present state of our knowledge to be the primary therapeutic actions of digitalis, but their secondary results are limited only by the conditions existing in the given case of heart-failure. By them the failing heart is restored and the circulation of blood through the body is improved.[8] The blood is more perfectly ventilated in the lungs; stasis and congestion are overcome; dyspnea, orthopnea, cyanosis and cough diminish and finally disappear; edema and transudates are absorbed; diuresis is produced.

[7] Influence of Digitalis on the T-wave of the Human Electrocardiogram, Jour. Exp. Med., 1915, xxi, 593.

[8] Stewart, G. N., and Scott, R. W.: Change Produced in the Bloodflow (in the Hands) under the Influence of Digitalis in Cases of Auricular Fibrillation, Jour. Pharm. and Exp. Therap., 1915, vii, 263.

Before leaving the subject of the clinical pharmacology of digitalis a few matters demand brief discussion because they do not even yet seem to be clearly understood by all. The impression that the existence of a high systolic blood-pressure in a patient with heart-failure contra-indicates the administration of digitalis seems still to linger in the minds of many. The subject of the influence of digitalis on the blood-pressure in man was discussed a few years ago,[9] and it was shown that the vasoconstriction which could be demonstrated to occur in animals and in isolated surviving vessels under the influence of digitalis took place only when amounts of the drug were used which were far in excess of any which could possibly be given to man. It was shown that there is no evidence that either digitalis or digitoxin has any direct action on the bloodvessels when given to man even in large therapeutic doses. A large number of careful observations of the effects of the administration upon the blood-pressure in man were analyzed and it was found that the changes in the systolic and diastolic pressures are generally relatively slight, the tendency being for the pressures to be altered in the direction of the normal. There is a marked tendency for the pulse-pressure—the difference between the systolic and diastolic pressures—to increase under the influence of digitalis, chiefly through reduction of the diastolic pressure, in cases of heart-failure in which the failure is relieved. A decided fall in the systolic pressure is to be anticipated when digitalis relieves heart-failure in cases in which it is accompanied by a high systolic pressure and marked edema. There is also a marked tendency for digitalis to reduce the systolic pressure from its high level in cases with marked dyspnea, cyanosis and circulatory stasis. All of the facts, therefore, show conclusively that digitalis is not contra-indicated by the existence of high blood-pressure.

A closely related matter is that of the possible action of digitalis on the human coronary arteries. Of course, it is not feasible to detect such an action with certainty in man, yet some recent text-books state that, in toxic doses at least, digitalis may produce a dangerous constriction of the coronaries, and it has also been argued that when pulsus alternans is produced or aggravated by digitalis the phenomenon is due to coronary constriction. These beliefs have also been responsible for the view that digitalis is contra-indicated in cases with so-called angina pectoris. We are convinced that these ideas are misleading and erroneous: (1) The painstaking animal experiments of Felix Meyer[10] and of Sakai and Saneyoshi[11]

[9] Eggleston, Cary: Influence of Large Doses of Digitalis and Digitoxin on the Blood-pressure in Man, Jour. Am. Med. Assn., 1917, lxix, 951.

[10] Ueber die Wirkung verschiedener Arzneimittel auf die Coronargefaesse des lebenden Tieres, Arch. f. Anat. and Phys., phys. Abteil., 1912, 223.

[11] Ueber die Wirkung einiger Herzmittel auf die Koronargefaesse, Arch. exp. Path. and Pharm., 1914–15, lxxviii, 331.

and others have shown that the digitalis bodies do not constrict the coronaries of the heart *in situ*. In fact, digitalis seems to dilate them actively while strophanthin increases the coronary blood flow indirectly by elevation of the aortic pressure. (2) The statement that marked coronary constriction may occur in man from toxic doses of digitalis is based upon pure assumption and not upon any satisfactory evidence. (3) The occurrence or aggravation of pulsus alternans occasionally seen in cases of advanced heart failure under digitalis treatment does not prove that the drug is responsible for the change or that coronary constriction is present. Pulsus alternans may well develop spontaneously in such cases and in spite of the administration of digitalis rather than because of it. When alternans is already present it is strong evidence that the exhaustion of the heart is almost complete, and in such a heart the exhaustion may progress even when digitalis is being used in adequate doses for all forms of treatment frequently fail to check the progress of failure in such late stages of heart disease. (4) Digitalis is often of great value in cases with pulsus alternans and not infrequently restores the normal rhythm, at least temporarily.[12] (5) When the administration of digitalis results in the relief of heart-failure and the restoration of cardiac efficiency it is inconceivable that it should improve the capacity of the heart for work and at the same time reduce and impair its nutrition and internal respiration by a constriction of the coronaries. It is a fact also that anginal pain is usually but a symptom of heart-failure and the control of the failure by the administration of digitalis frequently relieves the pain. In such cases the continued or intermittent use of digitalis, by preventing the recurrence of failure, often also prevents the recurrence of the pain.

The third question upon which some doubt seems to persist is that of the mechanism of the diuretic action of digitalis. While it has been claimed that digitalis exerts a specific diuretic action on the kidneys, or that it produces diuresis by selective vasodilatation of the renal arterioles, the evidence for these claims is quite unsatisfactory, and careful studies have shown conclusively that the drug is not a diuretic in normal animals. It has also been observed repeatedly that no diuresis follows the administration of digitalis to normal human beings or to those with heart-failure uncomplicated with edema or serous effusions. In cases of nephritis with edema, or even with general anasarca, digitalis also produces no diuresis when heart-failure is not associated with the nephritis. When, however, heart-failure is accompanied with edema or anasarca profuse diuresis may follow the administration of digitalis, but this is found to occur only when the heart-failure is more or less effectively

[12] Windle, J. D.: Clinical Observations on the Effect of Digitalis in Heart Disease with Pulsus Alternans, Quart. Jour. Med., 1916–17, x, 274.

overcome by the drug, and when the heart failure is not affected no diuresis ensues from its administration. It is clear, then, that the diuretic action of digitalis in man is essentially secondary to its capacity to relieve heart-failure and restore the circulation; and when it is effective in edematous cases of heart-failure, it is often one of the earliest of the manifestations of the action of the drug, though other evidences can be detected if looked for. When adequate digitalization fails to produce diuresis in a patient with edema and heart-failure it will almost invariably be found that either the heart-failure has not been relieved or that the failure is complicated by nephritis, which then demands appropriate treatment.

Having reviewed some of the more important therapeutic actions of digitalis, let us now turn to the consideration of certain of the problems connected with its oral administration to man. In approaching these questions we must bear in mind the following points:

1. The indication for the administration of digitalis is determined by the degree of heart-failure, not by the cause of the failure.

2. The dosage and the criteria of the action of digitalis are identical, irrespective of the cause of the heart-failure, although the method of administration may be influenced by the cause of the failure.

3. In the absence of satisfactory therapeutic response one can be certain that digitalis has been given a fair trial only when it has been administered to the point of production of one or more of the criteria of minor intoxication.

The proper administration of digitalis demands the ability to judge the degree of digitalization which is being produced because all of the digitalis bodies can cause serious poisoning and because the nature of heart-failure is such that incomplete recovery or death may result from inadequate treatment. The following are the more important criteria by which the degree of digitalization can be judged:

In cases which respond favorably there is a group of phenomena, both subjective and objective, which indicate more or less effective digitalization and which may be embraced by the term, "Clinical Improvement." These include all such definite evidences of improvement in the circulation as relief or disappearance of the patient's respiratory symptoms; relief of cardiac or precordial pain; disappearance of the nausea due to splanchnic congestion; the production of diuresis; diminution or disappearance of evidences of congestion of the liver; fall in pulse-rate; decreased degree of irregularity in auricular fibrillation together with reduction in the pulse deficit, or its disappearance.

The number and nature of these phenomena and the extent

of their development depend on the conditions existing prior to treatment, on the capacity of the heart to respond to digitalis and on the adequacy of treatment. When well-developed they usually indicate adequate digitalization and the discontinuance of the drug or a reduction in its dose. Their occurrence also corresponds in the majority of cases to the appearance of minor toxic actions of digitalis.

The following phenomena occur independently of a therapeutic response and are not necessarily indicative of a toxic action of digitalis, though each is certain evidence of the absorption and action of the drug: Prolongation of the time of auriculoventricular conduction, which can be detected in graphic records as one of the earliest and most constant effects of digitalis upon the heart; flattening or inversion of the *T* wave of the electrocardiogram, which is nearly as constant as the preceding but does not occur quite so early; the production of sinus arrhythmia or the exaggeration of a preëxisting sinus arrhythmia.

Finally, the following phenomena are indicative of some degree of digitalis intoxication and their appearance demands the cessation of further administration or a sharp reduction in the dose: Nausea or vomiting; marked grade of sinus arrhythmia, especially when phasic in type and independent of respiration; partial or complete heart-block; premature contractions; the "coupled rhythm" due to the regular recurrence of a premature contraction after each regular beat; auriculoventricular dissociation; the *A–V* or nodal rhythm; ventricular tachycardia; other rare disturbances of the cardiac rhythm. Two or more of these phenomena not infrequently occur together in the same patient.

These arrhythmias of digitalis intoxication must be distinguished from those due to the heart-failure itself. This can frequently be accomplished only as the result of the most careful and constant observation of the patient from the outset, usually with the aid of graphic records, for it is impossible to distinguish without knowledge of the previous condition whether block, premature contractions, etc., are due to digitalis or to the progress of the heart-failure. In cases of advanced heart-failure in which the administration of digitalis must always be carried to the limits of the patient's tolerance when the desired therapeutic effects are not obtained, the knowledge and skill of the clinician are frequently taxed to the limit to determine when to stop the administration of the drug. In all such cases it is best to secure the aid of a specialist, preferably from the beginning, but always before it is too late for his services to be of value.

While it is generally desirable in the treatment of heart-failure to secure the maximal therapeutic effects of digitalis promptly the urgency of the symptoms and various other factors must determine the rapidity with which digitalization should be induced in any

given patient. With this in mind, and in view of the facts already set forth, three general plans of dosage by oral administration are suggested.

Small Dose Method. From four to six days are generally required for digitalization by this method; $\frac{1}{8}$ to $\frac{1}{4}$ gram (gr. ij to gr. iv) of the powdered leaf or $1\frac{1}{4}$ to $2\frac{1}{2}$ c.c. (♏ xx to ♏ xl) of the tincture should be administered every four hours—four doses daily—and continued until digitalization is induced. With weak or poorly absorbed specimens of digitalis full digitalization may not be secured at all by this method or it may require ten days or more to secure it.

Large Dose Method. From one to two days are required for digitalization. During the first twenty-four hours a dose of $\frac{4}{10}$ gram (gr. vj to gr. vij) of the powdered leaf or 4 c.c. (dram j) of the tincture should be administered every six hours, day and night, for four doses. On the second day the dose should be reduced one-half and the interval may be shortened to four hours, giving four doses per day and none at night. This latter dose and interval should be continued until full digitalization is secured.

The Body Weight Method. This method permits full digitalization within ten to twenty hours from the beginning of administration and is specially serviceable in cases manifesting urgent symptoms. Its use has proved so satisfactory during the five years that have elapsed since its introduction that it has been possible very largely to do away with the necessity for the intravenous or intramuscular administration of ouabain, strophanthin or other digitalis preparation. It has been described in detail so recently that it is sufficient to refer to some of the published papers in which it is discussed.[13] [14] [15] [16]

Mention of other members of the digitalis group of drugs has been omitted in discussing dosage by oral administration, because digitalis itself is preëminently the drug of choice by reason of its availability, absorbability and persistence of action. Its availability needs no comment but a few remarks are in place with reference to the choice of preparation. The preparation selected should always be one which has been assayed biologically and proved to be of high activity. It should be remembered, however, that the biologic unit is a more or less arbitrary figure which merely serves to indicate the relative activity of the preparation, as determined by a particular method of assay, and in general it bears no direct relation to the dose

[13] Eggleston, Cary: Digitalis Dosage, Arch. Int. Med., 1916, xvi, 1.

[14] White, S. M., and Morris, R. E.: Eggleston Method of Administering Digitalis, Arch. Int. Med., 1918, xxi, 740.

[15] Robinson, G. C.: Rapidity and Persistence of the Action of Digitalis on Hearts showing Auricular Fibrillation, Am. Jour. Med. Sc., 1920, clix, 121.

[16] Eggleston, Cary: Administration of Digitalis by the "Eggleston Method," Jour. Am. Med. Assn., 1920, lxxiv, 733.

of the preparation for man. The cat unit, however, is employed for the calculation of the human dose in the Body Weight method of administration. The figures obtained by different methods of bio-assay are not comparable one with another, but it is generally true that a preparation which is highly active, as shown by one method, will be found active by any other, although the activity of a given specimen may differ considerably by different methods of assay.

The particular official form of digitalis selected will depend largely upon the personal preference of the physician, but we are convinced that the powdered leaf and the tincture are the most satisfactory. The dose of each is of convenient bulk; each can be assayed biologically and each keeps for long periods of time without material loss of activity. The powdered leaf is especially to be commended because it can be dispensed in capsules, which are easily carried and pleasant to take, and the disagreeable bitter taste of the fluid preparations is avoided. The dose of the fluidextract is too small for convenience, while that of the infusion is unnecessarily large, in view of its unpleasant flavor. Further the fluidextract is seldom up to standard in activity and the infusion is not assayed. Even when the infusion is prepared from the assayed leaf the activity of different lots is seldom uniform on account of variations in the completeness of extraction of the active constituents.

Of the many proprietary preparations and specialties which are offered with high claims for oral administration none is superior to the powdered leaf or tincture of high grade, and most are decidedly inferior. All are quite costly and the price of some is exorbitant. If one feels impelled to employ one of these, digipuratum or digipoten will be found to be the best, but these are merely carefully assayed, purified preparations from good digitalis leaves.

The materia medica of the digitalis group of drugs is large, but digitalis alone is well absorbed from the alimentary tract of man. Strophanthus, convallaria, squills, etc., are both poorly and irregularly absorbed. Strophanthus deserves special mention, because it is 100 times as active as digitalis, yet the official dose is only half that of digitalis, and it is often given in equal doses. The irregularity of its absorption is of greater importance than the fact that its absorption is generally poor, for in some cases serious poisoning has resulted from the rapid absorption of the customary dose.[17] We are convinced that strophanthus should never be used for oral administration to man on account of the danger of serious accident, despite the fact that it often has been so used with satisfactory results.

The subjects of absorption, persistence of action and elimination of digitalis are so closely related that we will discuss them together

[17] Hatcher, R. A., and Bailey H. C.: Clinical Use of Strophanthus, Jour. Am. Med. Assn., 1910, lv, 1697.

in the closing section of this discourse. While digitalis is generally well-absorbed from the human alimentary canal, several instances have come to our attention in which absorption was very unsatisfactory.[18] In some instances the poor absorption is unquestionably due to some individual peculiarity on the part of the patient or to some factor in his condition. In others, however, the fault seems to lie with the digitalis, and my colleague, Dr. Robert A. Hatcher, has been able to throw some light on this matter. His work has not yet been published and is still incomplete, but the following observations seem highly significant: Digitalis can be readily separated into two fractions by extraction of its aqueous solution with chloroform. The chloroform-soluble fraction is readily absorbed from the alimentary tract of the cat, while the chloroform-insoluble fraction is poorly and irregularly absorbed. Both fractions are active when injected intravenously, manifesting the typical actions of digitalis. The two fractions vary widely in the relative proportions in which they are present in different samples of digitalis, and at least one of the samples of digitalis which showed very poor absorption in man contained relatively very little of the chloroform-soluble, absorbable fraction.

Dr. Hatcher has supplied me with solutions of these two fractions, of equal activity by the cat test, and these have been administered to a number of patients to observe their absorption. These observations, too, are incomplete, but they have shown quite definitely that the chloroform-soluble fraction is well absorbed from the human alimentary tract while the chloroform-insoluble fraction is absorbed poorly. Comparing the amounts required to produce minor intoxication or full therapeutic effects, nearly four times as much of the chloroform-insoluble fraction as of the chloroform-soluble is required to produce similar effects. This is true even when the two fractions are given on different occasions to the same patient. The rate of absorption of the chloroform-soluble fraction seems to be quite equal to that of the best digitalis, but we do not yet know that it is any more rapid. The results of these observations will be reported in detail at a later time.[19]

It has been shown that digitalis of high grade is generally well absorbed from the digestive tract of man, and it seems apparent that the absorption of a single dose is completed within six hours. Recently, Pardee (unpublished) has shown that there is definite electrocardiographic evidence of considerable absorption in from two to four hours, and the observations of Levy (unpublished) and

[18] Wedd, A. M.: Observations on the Clinical Pharmacology of Digitalis, Bull. Johns Hopkins Hosp., 1919, xxx, 131.

[19] Since this was written two preliminary papers have appeared on this work: Hatcher, Robert A., Some Observation on the Pharmacology of a Digitalis Body, Jour. Am. Med. Assn., 1920, lxxv, 460. Eggleston, Cary, The Absorption of a Digitalis Body, Jour. Am. Med. Assn., 1920, lxxv, 463.

of Robinson[20] confirm this. These observations are quite at variance with the rather general belief that digitalis is slowly absorbed. That belief seems to have been based on the older mistaken idea that from three to six days were always required to secure digitalization in man, which, in turn, arose from the administration of single doses which were too small. We know now that digitalis is fairly rapidly absorbed and that full digitalization can be secured by oral administration certainly within twenty-four hours after the first dose, and frequently within ten hours.

Through the work of Hatcher[21] on animals and of Eggleston,[22] Cohn and his associates, Robinson and others, on man, it has been proved that the action of digitalis on the human heart may persist for periods up to two weeks or longer after administration has been stopped. This persistence of action is one of the valuable features of digitalis as a cardiac remedy and its recognition is of considerable therapeutic importance. In the first place it accounts for the phenomenon previously called "cumulation," and always somewhat shrouded in mystery. Taken together with the knowledge of the rate of absorption of digitalis, and of its average dose for man, it demonstrates the fact that it is quite unnecessary to administer digitalis at the short intervals customarily observed. It is never necessary to administer a dose more often than every four hours, and a six-hour interval is generally preferable. Further, when a patient is to be kept upon the continuous administration of a small dose of digitalis this need be taken only once daily instead of being divided into two or three doses. Finally, the persistence of action must always be kept in mind when one considers the administration of ouabain (crystalline strophanthin) or amorphous strophanthin intravenously or intramuscularly, for the doses of the latter are commonly large, in terms of activity, and serious or fatal poisoning has occurred from such injections in patients who have recently been receiving digitalis.

The mechanism of this persistent action is not definitely understood, but the evidence seems to indicate that it is due to the firm fixation of a small amount of the drug in the tissues of the heart where it continues to exert its actions. One of the strongest reasons for believing this to be the case is the fact that digitalis disappears from the blood stream very rapidly after intravenous injection in a variety of animals. Some earlier pharmacologic experiments also seem to indicate that the heart is capable of storing minute quantities of the digitalis bodies.

Very recently Pardee[23] has studied the rate of the elimination

[20] Loc. cit.

[21] Persistence of the Action of the Digitalins, Arch. Int. Med., 1912, x, 268.

[22] Clinical Observations on the Duration of Digitalis Action, Jour. Am. Med. Assn., 1912, lix, 1352.

[23] Notes on Digitalis Medication, Jour. Am. Med. Assn., 1919, lxxiii, 1822.

of digitalis in man by administering the drug orally until a definite effect was produced and determining the dose required. After a lapse of an interval during which no digitalis was administered the same preparation was again given and the amount determined which was required to reinduce the effect previously produced, In this way, using a single sample of tincture of digitalis, he determined that the rate of elimination amounted to about twenty-two minims per day. This figure, of course, applies only to the particular specimen of digitalis with which he worked, but it is significant and agrees with the general impression that from $1\frac{1}{2}$ to 2 grains of digitalis (15 to 20 minims of the tincture) can generally be administered over long periods of time to prevent the recurrence of heart-failure, and without producing intoxication.

Finally, in closing, let me refer briefly to the investigations of Hatcher and Eggleston[24] on the elimination of certain digitalis bodies from the animal organism, since they throw some light on the mechanism by which elimination is accomplished. Their investigations show that in animals at least both the liver and the kidneys participate. The liver seems to be capable of rapidly fixing, and probably also of destroying or decomposing, a large proportion of ouabain after its entrance into the blood stream. Other tissues in the body also apparently can fix rapidly and thereby remove from the blood stream large amounts of ouabain, but the liver seems to be the organ chiefly concerned in the elimination. The part played by the kidneys is normally relatively insignificant. Whether or not these are the mechanisms involved in man is not known, and at the present time there seems to be no method of attacking the problem in the human being.

ROENTGENOLOGICAL ASPECTS OF LOWER RIGHT QUADRANT LESIONS.[1]

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The diagnosis of lower right quadrant lesions is a matter of great importance; not only is this because of the frequent occurrence of appendicitis, but because of other lesions which are apt to present

[24] Studies in the Elimination of Certain of the Digitalis Bodies from the Animal Organism, Jour. Pharm. and Exp. Therap., 1919, xii, 405.

[1] Read at the meeting of the American Gastro-enterological Association, Atlantic City, May 3, 1920.